Practitioner's Docket No. R00208US (#90568)

CHAPTER II

Preliminary Classification:
Proposed Class: 604
Subclass: 890.1

NOTE: "All applicants are requested to include a preliminary classification on newly filed patent applications. The preliminary classification, preferably class and subclass designations, should be identified in the upper right-hand corner of the letter of transmittal accompanying the application papers, for example 'Proposed Class 2, subclass 129.'" M.P.E.P., § 601, 7th ed.

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US)

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/03922	8 JUNE 1999	25 JUNE 1998

TITLE OF INVENTION: TRANSDERMAL THERAPEUTIC SYSTEM CONTAINING HORMONES AND CRYSTALLIZATION INHIBITORS

APPLICANT(S): KLEIN, Robert Peter; MECONI, Reinhold and MULLER, Walter

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231

ATTENTION: EO/US

CERTIFICATION UNDER 37 C.F.R. § 1.10*
(Express Mail label number is mandatory.)
(Express Mail certification is optional.)

I hereby certify that this Transmittal Letter and the papers indicated as being transmitted therewith is being deposited with the United States Postal Service on this date DECEMBER 22, 2000, in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EK980729435US, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

CHRISTINE A. KOTRAN
(type or print name of person mailing paper)
Christine A. Kotran
Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. § 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

***WARNING:** Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

NOTE: To avoid abandonment of the application, the applicant shall furnish to the USPTO, not later than 20 months from the priority date: (1) a copy of the international application, unless it has been previously communicated by the International Bureau or unless it was originally filed in the USPTO; and (2) the basic national fee (see 37 C.F.R. § 1.492(a)). The 30-month time limit may not be extended. 37 C.F.R. § 1.495.

WARNING: *Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. § 1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing—See 37 C.F.R. § 1.8.*

NOTE: Documents and fees must be clearly identified as a submission to enter the national state under 35 U.S.C. § 371 otherwise the submission will be considered as being made under 35 U.S.C. § 111. 37 C.F.R. § 1.494(f).

I. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. § 371:

a. ☒ This express request to immediately begin national examination procedures (35 U.S.C. § 371(f)).

b. ☒ The U.S. National Fee (35 U.S.C. § 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

(Transmittal Letter to the United States Elected Office (EO/US) **[13-18]**—page 2 of 8)

2. Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
XXXX	TOTAL CLAIMS 14	−20=	---	× $18.00=	$ ---
	INDEPENDENT CLAIMS 2	−3=	---	× $78.00=	---
	MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	---
BASIC FEE**	☐ U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an International preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: ☐ and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(1) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 C.F.R. § 1.492(a)(4)) ..... $96.00 ☐ and the above requirements are not met (37 C.F.R. § 1.492(a)(1)) ..... $670.00 XXXX U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the U.S. PTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U.S. PTO: ☐ has been paid (37 C.F.R. § 1.492(a)(2)) ..... $690.00 ☐ has not been paid (37 C.F.R. § 1.492(a)(3)) ..... $970.00 XXXX where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 C.F.R. § 1.492(a)(5)) ..... ~~$840.00~~ $860.00				860.00
	Total of above Calculations				= 860.00
SMALL ENTITY	Reduction by 1/2 for filing by small entity, if applicable. Affidavit must be filed also. (note 37 C.F.R. § 1.9, 1.27, 1.28)				− ---
	Subtotal				860.00
	Total National Fee				$ 860.00
	Fee for recording the enclosed assignment document $40.00 (37 C.F.R. § 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				---
TOTAL	Total Fees enclosed				$ 860.00

*See attached Preliminary Amendment Reducing the Number of Claims.

i. XXX A check in the amount of $860.00 to cover the above fees is enclosed.

ii. ☐ Please charge Account No. _____ in the amount of $ _____. A duplicate copy of this sheet is enclosed.

**WARNING: *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b).*

WARNING: *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F.R. § 1.495(b)(2). The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

3. ☒ A copy of the International application as filed (35 U.S.C. § 371(c)(2)):

NOTE: *Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment. "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below.*

a. ☒ is transmitted herewith.

b. ☐ is not required, as the application was filed with the United States Receiving Office.

c. ☐ has been transmitted

i. ☐ by the International Bureau.
Date of mailing of the application (from form PCT/1B/308): _____.

ii. ☐ by applicant on _____.
Date

4. ☒ A translation of the International application into the English language (35 U.S.C. § 371(c)(2)):

a. ☒ is transmitted herewith.

b. ☐ is not required as the application was filed in English.

c. ☐ was previously transmitted by applicant on _____.
Date

d. ☐ will follow.

5. ☒ Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. § 371(c)(3)):

NOTE: The Notice of January 7, 1993 points out that 37 C.F.R. § 1.495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended. The Notice further advises that: "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1.121. In many cases, filing an amendment under section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 36.

a. ☐ are transmitted herewith.

b. ☐ have been transmitted

i. ☐ by the International Bureau.
Date of mailing of the amendment (from form PCT/1B/308): _____.

ii. ☐ by applicant on (date) _____.
Date

c. ☒ have not been transmitted as

i. ☒ applicant chose not to make amendments under PCT Article 19.
Date of mailing of Search Report (from form PCT/ISA/210.): 27 DECEMBER 1999

ii. ☐ the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. ☒ A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. § 371(c)(3)):

a. ☐ is transmitted herewith.

b. ☐ is not required as the amendments were made in the English language.

c. ☒ has not been transmitted for reasons indicated at point 5(c) above.

7. ☒ A copy of the international examination report (PCT/IPEA/409)

☒ is transmitted herewith.

☐ is not required as the application was filed with the United States Receiving Office.

8. ☒ Annex(es) to the international preliminary examination report

a. ☒ is/are transmitted herewith.

b. ☐ is/are not required as the application was filed with the United States Receiving Office.

9. ☒ A translation of the annexes to the international preliminary examination report

a. ☒ is transmitted herewith.

b. ☐ is not required as the annexes are in the English language.

10. [X] An oath or declaration of the inventor (35 U.S.C. § 371(c)(4)) complying with 35 U.S.C. § 115

a. ☐ was previously submitted by applicant on _____. Date

b. ☐ is submitted herewith, and such oath or declaration

i. ☐ is attached to the application.

ii. ☐ identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. § 1.70.

c. [X] will follow.

II. Other document(s) or information included:

11. [X] An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):

a. [X] is transmitted herewith.

b. ☐ has been transmitted by the International Bureau. Date of mailing (from form PCT/IB/308): _____.

c. ☐ is not required, as the application was searched by the United States International Searching Authority.

d. ☐ will be transmitted promptly upon request.

e. ☐ has been submitted by applicant on _____. Date

12. ☐ An Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98:

a. ☐ is transmitted herewith.

Also transmitted herewith is/are:

☐ Form PTO-1449 (PTO/SB/08A and 08B).

☐ Copies of citations listed.

b. ☐ will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. § 371(c).

c. ☐ was previously submitted by applicant on _____. Date

13. ☐ An assignment document is transmitted herewith for recording.

A separate ☐ "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or ☐ FORM PTO 1595 is also attached.

_____

_____

_____

14. ☒ Additional documents:

a. ☐ Copy of request (PCT/RO/101)

b. ☒ International Publication No. WO 99/66901

i. ☐ Specification, claims and drawing

ii. ☒ Front page only

c. ☒ Preliminary amendment (37 C.F.R. § 1.121)

d. ☒ Other

Notification of the Recording of a Change (re applicant's name and address); Written Opinion and response thereto; and ~~transmittal for IPER (PCT/IPEA/416)~~

15. ☒ The above checked items are being transmitted

a. ☒ before 30 months from any claimed priority date.

b. ☐ after 30 months.

16. ☐ Certain requirements under 35 U.S.C. § 371 were previously submitted by the applicant on _____, namely:

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependant claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).

NOTE: "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).

☒ The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 08-2441.

☒ 37 C.F.R. § 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. § 1.495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

☒ 37 C.F.R. § 1.492(b), (c) and (d) (presentation of the claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action.

☒ 37 C.F.R. § 1.17 (application processing fees)

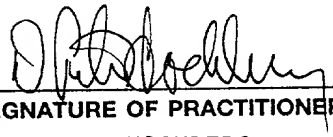
☒ 37 C.F.R. § 1.17(a)(1)–(5) (extension fees pursuant to § 1.136(a).

☐ 37 C.F.R. § 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. § 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).

NOTE: 37 C.F.R. § 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

☐ 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).



SIGNATURE OF PRACTITIONER

Reg. No.: 24,603

D. PETER HOCHBERG

(type or print name of practitioner)

Tel. No.: (216) 771-3800

D. PETER HOCHBERG COL., L.P.A.

P.O. Address

Customer No.:

1940 E. 6TH STREET - 6TH FLOOR

CLEVELAND, OH 44114-2294

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Robert Klein, Reinhold Meconi, Walter Müller

Serial No. :

Filed : (Herewith)

Title : TRANSDERMAL THERAPEUTIC SYSTEM CONTAINING HORMONES AND CRYSTALLIZATION INHIBITORS

Attorney File : RO0208US (#90568)

Box PCT
Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to substantive examination of the above-identified application, please amend the application, without prejudice, as follows:

In the specification:

Page 1, in the center of the page after the title and before the first line of text (line 4), insert -- BACKGROUND OF THE INVENTION -- ; at the left-hand margin before the first line of text, insert -- Field of the Invention -- ; at the left-hand margin between lines 7 and 8, insert -- Description of the Prior Art --.

Page 2, in the center of the page between lines 10 and 11, insert -- SUMMARY OF THE INVENTION --.

Page 4, in the center of the page between lines 19 and 20, insert -- DESCRIPTION OF THE PREFERRED EMBODIMENT --.

Page 7, after the last line, insert the following paragraph:

-- The invention has been described with particular emphasis on the preferred

embodiments, but variations and modifications within the spirit and scope of the invention may occur to those skilled in the art to which the invention pertains. --

In the claims:

Claim 1, line 4, after the word "ingredients", insert -- and containing oestradiol and norethisterone acetate, -- ; delete "which", insert -- said reservoir -- ; line 5, after and, insert -- is -- ; line 8, delete "characterized in that" and insert -- wherein -- .

Claim 2, line 2, delete "characterized in that" and insert -- wherein -- ; lines 4-5, delete "in particular in" and insert -- said polymers having -- .

3. (Amended) Transdermal therapeutic system according to [either of] Claim[s 1 and 2,] 1, [characterized in that] wherein the reservoir comprises at least one [or more] crystallization inhibitor[s] in a proportion of from 0.05[-] to 30% by weight.

4. (Amended) Transdermal therapeutic system according to [one or more of] Claim[s 1 to 3,] 1, [characterized in that] wherein the reservoir comprises oestradiol and norethisterone acetate in a weight ratio of from 1:2 to 1:15, [preferably from 1:3 to 1:7,] and in an overall concentration of up to 25% by weight.

Claim 5, lines 1-2, delete "one or more of Claims 1 to 4" and insert -- Claim 1 -- ; line 2, delete "characterized in that" and insert -- wherein -- ; line 3, after the word "group", insert -- consisting -- .

Claim 6, lines 1-2, delete "one or more of Claims 1 to 5" and insert -- Claim 1 -- ; line 2, delete "characterized in that" and insert -- wherein -- ; line 3, after the text "adhesive is", insert -- selected from the group consisting of -- ; line 4, delete "or" and insert -- and -- .

Claim 7, lines 1-2, delete "one or more of Claims 1 to 6" and insert -- Claim 1 -- ; line 2, delete "characterized in that" and insert -- wherein -- ; line 3, delete " two or more" and insert -- at least two -- .

8. (Amended) Transdermal therapeutic system according to [one or more of] Claim[s 1 to 7,] 1, [characterized in that] wherein the reservoir has a layer thickness of 0.02 mm[-] to 0.500 mm[, preferably 0.030-0.200 mm].

Claim 9, lines 1-2, delete "one or more of Claims 1 to 8" and insert -- Claim 1 -- ; line 2, delete "characterized in that" and insert -- wherein -- ; line 4, delete "and/or with a pressure-sensitive adhesive margin".

Please delete claim 10.

Please insert the following new claims:

-- 11. Transdermal therapeutic system according to claim 4, wherein the reservoir comprises oestradiol and norethisterone acetate in a weight ratio of from 1:3 to 1:7. --

-- 12. Transdermal therapeutic system according to Claim 8, wherein the reservoir has a layer thickness of 0.030-0.200 mm. --

-- 13. Transdermal therapeutic system according to Claim 9, wherein the reservoir is provided with a pressure-sensitive adhesive margin. --

-- 14. Transdermal therapeutic system according to Claim 1, wherein the reservoir is provided with a pressure-sensitive adhesive margin. --

-- 15. A method for providing therapeutic applications in human medicine, said method comprising controlling the release of oestradiol in combination with norethisterone acetate to the human skin. --

REMARKS

Please note that an IPE Written Opinion (PCT/IPEA/408) was issued May 26, 2000 by the German PCT office. In response to this, an amendment was submitted on August 24, 2000 which contains an amended claim 1; that amended claim 1 is not incorporated herein. Instead,

the original claim 1 is amended in this preliminary amendment.

The foregoing amendments to the application are made to place it in conformance with U.S. patent practice and to delete multiple-dependencies in the claims, thus reducing the government filing fee. Accordingly, prosecution on the merits hereof is respectfully requested.

Respectfully submitted,

By:_____
D. Peter Hochberg
Reg. No. 24,603

DPH/ KRV
Enc.

D. Peter Hochberg Co., L.P.A.
The Baker Building - 6th Floor
1940 East 6th Street
Cleveland, Ohio 44114
(216) 771-3800

EXPRESS MAIL CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that the foregoing Preliminary Amendment and any document(s) referred to as attached hereto is being deposited with the United States Postal Service on the date indicated below in an envelope as "Express Mail Post Office to Addressee" service mailing Label Number EK980729435US addressed: Box PCT, Commissioner for Patents, Washington, D.C. 20231.

Date: 12/22/2000

Christine A. Kotran

PCT

Attorney Docket No. RO0208US (#90568)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Robért Klein, Reinhold Meconi, Walter Müller
Serial No.	:	09/720,287
I.A. Filing Date	:	June 8, 1999
Title	:	TRANSDERMAL THERAPEUTIC SYSTEM CONTAINING HORMONES AND CRYSTALLIZATION INHIBITORS
Attorney File	:	RO0208US (#90568)

Commissioner for Patents
Washington, D.C. 20231

SECOND PRELIMINARY AMENDMENT

Dear Sir:

Preliminary to the substantive examination of the above-identified application, please amend the application as follows:

IN THE SPECIFICATION:

Page 3, the third complete paragraph beginning on line 12:

Suitable ageing inhibitors, plasticizers, antioxidants and absorption improvers are known to the person skilled in the art and are described, for example, in DE 37 43 946.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Robert Klein, Reinhold Meconi, Walter Müller

Serial No. : 09/720,287

REMARKS

The above-identified application contained an inadvertent clerical error in the specification in that one piece of prior art was incorrectly identified in the specification. The appropriate prior art referred to on page 3 of the original English translation of the application should be DE 37 43 946. Applicant respectfully requests that this information be corrected in the specification of this application.

Respectfully submitted,

By: _____
D. Peter Hochberg
Reg. No. 24,603

DPH/KRV

D. Peter Hochberg Co., L.P.A.
1940 East Sixth Street – 6th Floor
Cleveland, OH 44114-2294
(216) 771-3800

CERTIFICATE OF MAILING/TRANSMISSION (37 C.F.R. 1.8(a))

I hereby certify that this paper (along with any paper referred to as being transmitted therewith) is being deposited with the United States Postal Service on the date below as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231.

June 21, 2001
Date

Katherine R. Vieyra

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Robert Klein, Reinhold Meconi, Walter Müller
Serial No.	:	09/720,287
I.A. Filing Date	:	June 8, 1999
Title	:	TRANSDERMAL THERAPEUTIC SYSTEM CONTAINING HORMONES AND CRYSTALLIZATION INHIBITORS
Attorney File	:	RO0208US (#90568)

Commissioner for Patents
Washington, DC 20231

ATTACHMENT TO AMENDMENT

MARKED UP SPECIFICATION SHOWING CHANGES RELATIVE TO THE ORIGINAL VERSION

Page 3, the third complete paragraph beginning on line 12:

Suitable ageing inhibitors, plasticizers, antioxidants and absorption improvers are known to the person skilled in the art and are described, for example, in [DE 37 43 949] DE 37 43 946.

TRANSDERMAL THERAPEUTIC SYSTEM CONTAINING HORMONES AND CRYSTALLIZATION INHIBITORS

The invention relates to a transdermal therapeutic system (TTS) for controlled release of oestradiol in combination with norethisterone acetate to the human skin.

Oestradiol in combination with norethisterone acetate has a very low saturation solubility in the auxiliaries normally used to formulate transdermal therapeutic systems, such as polyacrylate adhesives, tackifiers, plasticizers and absorption improvers. As a result, the capacity to load a TTS with dissolved active ingredient is greatly limited, and/or, in the case of supersaturation, unwanted crystallization occurs during storage. Consequently, the proportion of dissolved active ingredients in the matrix is reduced, which has an adverse effect on their release.

For combined preparations comprising oestradiol and norethisterone acetate, administration forms have been developed in which the active ingredients in a transdermal therapeutic system are contained in separate areas. However, manufacturing such TTSs is very expensive.

Accommodating drying agents together with transdermal therapeutic systems in the primary packaging reduces the risk of recrystallization but is far from straightforward.

DE-A 43 36 557 describes an active substance transdermal therapeutic system based on a pressure-sensitive adhesive which comprises rosin esters. It is prepared by kneading the components in the melt at temperatures between 100 and 140°C and then carrying out coating. Such high temperatures in the preparation of pharmaceutical forms carry with them the risk that degradation products may be formed in an unacceptably high amount.

WO 95/30409 describes a topical polymer release system for the administration of certain active ingredients by means of a propellantless aerosol pump. The absence of adhesives is emphasized as an advantage. Additional components used include crystallization inhibitors/ stabilizers and/or penetration enhancers such as substituted cyclodextrins, Transcutol, urea and isoterpenes; the active substance combination of oestradiol and norethisterone acetate is not claimed.

It is therefore an object of the invention to provide a stable, i.e. recrystallization-free, plaster comprising the active ingredients oestradiol and norethisterone acetate.

It has surprisingly been found that in a transdermal therapeutic system having the features of the main claim this object is achieved by the use of an amino-containing polymer as crystallization inhibitor. Advantageous crystallization inhibitors used are polymers based on butyl methacrylate, 2-dimethylaminoethyl methacrylate and methyl methacrylate, preferably in a molar ratio of 1:2:1, polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines and polyglucosamines. It has been found that the crystallization inhibitors are particularly suitable in a proportion of from 0.05 to 30% by weight.

The formation of hydrogen bonds between the basic groups of the crystallization inhibitor and the mobile hydrogen atoms of the oestradiol molecule results in immobilization of oestradiol. Consequently, the concentration of freely mobile oestradiol in the matrix is reduced and crystallization prevented.

The pressure-sensitive adhesive reservoir contains oestradiol and norethisterone acetate in a weight ratio of from 1:2 to 1:15, preferably from 1:3 to 1:7, and in an overall concentration of up to 25% by weight.

The reservoir may comprise a constituent from the group consisting of ageing inhibitors, plasticizers, antioxidants and absorption improvers, the plasticizer being used in a concentration of from 0 to 5% by weight and the ageing inhibitor in a concentration of from 0.1 to 2% by weight.

Suitable ageing inhibitors, plasticizers, antioxidants and absorption improvers are known to the person skilled in the art and are described, for example, in DE 37 43 949.

In order to be able to apply the transdermal therapeutic system to the skin it is necessary for the system to have pressure-sensitive adhesive properties. In order to impart these properties to the transdermal therapeutic system of the invention use is made of polyacrylate pressure-sensitive adhesives in the form of solutions in organic solvents, known as solvent-based pressure-sensitive adhesives.

It is also possible to use polyacrylate pressure-sensitive adhesives in the form of aqueous dispersions.

Also suitable are hot-melt pressure-sensitive adhesives. These are free of solvent or dispersant and are applied from the melt.

UV-crosslinkable acrylate pressure-sensitive adhesives are also suitable. These are solvent-free and are applied using the conventional coating techniques. Subsequently, the polymer chains are crosslinked by irradiation with UV

light. This is necessary in order to give the pressure-sensitive adhesive adequate cohesion.

The reservoir of the transdermal therapeutic system may consist of a plurality of layers each with the same or different concentrations of active ingredient.

The layer thickness of the reservoir is from 0.02 mm to 0.500 mm but preferably from 0.030 mm to 0.200 mm.

The reservoir can be provided with an additional pressure-sensitive adhesive layer and/or with a pressure-sensitive adhesive margin. This becomes necessary when the pressure-sensitive adhesive properties of the reservoir itself are inadequate.

The transdermal therapeutic system of the present invention is intended for therapeutic applications in human medicine.

The invention is illustrated below on the basis of examples.

Example 1

155.08 g of Durotak 387-2287 (National Starch) (polyacrylate pressure-sensitive adhesive (PSA)) and
4.81 g of Eudragit E 100 (Röhm) (polyacrylate)

are homogenized with stirring and, together with a suspension of

2.17 g of Eutanol G (Caesar und Loretz) (long-chain fatty alcohol)
0.03 g of aluminium acetylacetonate (Merck-Schuchardt),
1.29 g of oestradiol hemihydrate and
8.33 g of norethisterone acetate,

are dissolved in a solvent mixture comprising

27.98 g   of ethyl acetate and
27.97 g   of ethanol.

The resultant adhesive solution is applied to a detachable protective layer of Hostaphan RN 100, siliconized on both sides, to give after drying an active substance matrix having a coated weight of 96.3 g/m². A backing layer impermeable to the active ingredients (0.015 mm thick polyester film) is laminated onto the resultant matrix. Subsequently, TTS patches measuring 40 cm² are punched out.

Examples 2-7 and comparison:

Preparation takes place as described under Example 1 but with the starting materials and amounts specified in Table 1.

Table 1: Composition [g]

Example	Comp-arison	2	3	4	5	6	7
Durotak 387-2287	424.31	132.84	162.25	171.50	171.50	162.25	171.50
Oestradiol hemihydrate	3.37	1.34	1.34	1.34	1.34	1.34	1.34
Norethister-one acetate	21.60	8.65	8.65	8.65	8.65	8.65	8.65
Eutanol G	5.59	2.25	2.25	2.25	2.25	2.25	2.25
Al acetyl-acetonate	1.36	0.054	0.054	0.054	0.054	0.054	0.054
Ethyl acetate		36.48	29.28	27.11	27.11	29.28	27.11
Ethanol		36.48	29.28	27.11	27.11	29.28	27.11
Methyl ethyl ketone	134.79	--	--	--	--	--	--
Euredur 145	--	20.0	--	--	--	--	--
Euredur 125	--	--	5.0	--	--	--	--
Euredur 250	--	--	--	0.5	--	--	--
Euredur 43	--	--	--	--	0.5	--	--
Euredur 27	--	--	--	--	--	5.0	--
Euredur 10	--	--	--	--	--	--	0.5

The test for signs of recrystallization was conducted microscopically in transmitted light at 40 times magnification. The results are set out in Table 2.

Table 2: Recrystallization

Example 1	Crystals per 40 cm^2 following storage for 3 months at 40°C
Comparison	154
1	0
2	0
3	0
4	0
5	0
6	0
7	0

As evident from Table 2 the addition of crystallization inhibitors gives transdermal therapeutic systems which are free from crystallization, in contrast to the comparative example (without crystallization inhibitor) in which there is considerable crystallization within a period of 3 months.

CLAIMS

1. Transdermal therapeutic system in plaster form for controlled release of oestradiol in combination with norethisterone acetate, comprising a backing layer, a reservoir supersaturated with active ingredients and containing estradiol and norethisterone acetate, which reservoir is attached to said backing layer and is prepared using polyacrylate pressure-sensitive adhesives and crystallization inhibitors, and a detachable protective layer, characterized in that the crystallization inhibitor is an amino-containing polymer.

2. Transdermal therapeutic system according to Claim 1, characterized in that the crystallization inhibitor is selected from polymers based on butyl methacrylate, 2-dimethylaminoethyl methacrylate and methyl methacrylate, in particular in a molar ratio of 1:2:1, polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines and polyglucosamines.

3. Transdermal therapeutic system according to either of Claims 1 and 2, characterized in that the reservoir comprises one or more crystallization inhibitors in a proportion of from 0.05-30% by weight.

4. Transdermal therapeutic system according to one or more of Claims 1 - 3, characterized in that the reservoir comprises oestradiol and norethisterone acetate in a weight ratio of from 1:2 to 1:15, preferably from 1:3 to 1:7, and in an overall concentration of up to 25% by weight.

5. Transdermal therapeutic system according to one or more of Claims 1 - 4, characterized in that the reservoir includes a constituent from the group of ageing inhibitors,

plasticizers, antioxidants and absorption improvers, the plasticizer being used in a concentration of 0-5% by weight and the ageing inhibitor in a concentration of 0.1-2% by weight.

6. Transdermal therapeutic system according to one or more of Claims 1 - 5, characterized in that the pressure-sensitive adhesive is a solvent-based adhesive, a dispersion adhesive, a hot-melt adhesive or a UV-crosslinkable adhesive.

7. Transdermal therapeutic system according to one or more of Claims 1 - 6, characterized in that the reservoir consists of two or more layers.

8. Transdermal therapeutic system according to one or more of Claims 1 - 7, characterized in that the reservoir has a layer thickness of 0.02 mm-0.500 mm, preferably 0.030-0.200 mm.

9. Transdermal therapeutic system according to one or more of Claims 1 - 8, characterized in that the reservoir is provided with an additional pressure-sensitive adhesive layer and/or with a pressure-sensitive adhesive margin.

10. Use of the transdermal therapeutic system corresponding to one or more of Claims 1-9 for therapeutic applications in human medicine.

ABSTRACT

A transdermal therapeutic system in plaster form for controlled release of oestradiol in combination with norethisterone acetate, comprising a backing layer, a reservoir supersaturated with active ingredients which is attached to said backing layer and prepared using polyacrylate pressure-sensitive adhesives and crystallization inhibitors, and a detachable protective layer, is characterized in that the crystallization inhibitor is an amino-containing polymer.

Attorney Docket No. **RO0208US (#90568)**

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL,CONTINUATION OR CIP)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type: (check one applicable item below)

( ) original
( ) design

NOTE: If the declaration is for an International Application being filed as a divisional, continuation or continuation-in-part application do not check any of next two items and check appropriate one of last three items.

(X) national stage of PCT
( ) supplemental

NOTE: If one of the following 3 items apply then complete and also attach ADDED PAGES FOR DIVISIONAL, CONTINUATION OR CIP.

( ) divisional
( ) continuation
( ) continuation-in-part (CIP)

INVENTORSHIP IDENTIFICATION

My residence, post office address and citizenship are as stated below next to my name, I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

TITLE OF INVENTION

TRANSDERMAL THERAPEUTIC SYSTEM CONTAINING HORMONES AND CRYSTALLIZATION INHIBITORS

SPECIFICATION IDENTIFICATION

the specification of which: (complete (a), (b), or (c))

(a) ( ) is attached hereto.
(b) ( ) was filed on as ( ) Serial No. or
( ) Express Mail No. , as Serial No. not yet known
and was amended on (if applicable).

(c) (X) was described and claimed in PCT International Application No. **PCT/EP99/03922** filed on **June 8, 1999** and as amended under PCT Article 19 on (if any).

ACKNOWLEDGEMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations. Sec. 1.56(a).

( ) In compliance with this duty there is attached an information disclosure statement. 37 CFR 1.97.

PRIORITY CLAIM

I hereby claim foreign priority benefits under Title 35, United States Code, Sec. 119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

(complete (d) or (e))

(d) ( ) no such applications have been filed.
(e) (X) such applications have been filed as follows

NOTE: Where item (c) is entered above and the International Application which designated the U.S. claimed priority check item (e), enter the details below and make the priority claim.

EARLIEST FOREIGN APPLICATION(S), IF ANY FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

COUNTRY	APPLICATION NO.	DATE OF FILING (month,day,year)	PRIORITY CLAIMED UNDER 37 USC 119
			( ) YES NO ( )
			( ) YES NO ( )
			( ) YES NO ( )

ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

German Appln. 198 28 273.7 filed June 25, 1998
and
PCT Appln. PCT/EP99/03922 filed June 8, 1999

POWER OF ATTORNEY

As a named inventor, I hereby appoint D. Peter Hochberg, Reg. No. 24,603, Katherine R. Vieyra, Reg. No. 47,155, and William H. Holt, Reg. No. 20,766, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

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CHECK PROPER BOX(ES) IF ANY OF THE FOLLOWING ADDED PAGE(S) FORM A PART OF THIS DECLARATION

( ) Signature for third and subsequent joint inventors. Number of pages added _____ .

( ) Signature by administrator(trix), executor(trix) or legal representative of deceased or incapacitated inventor. Number of pages added _____ .

( ) Signature for inventor who refuses to sign or cannot be reached by person authorized under 37 CFR 1.47. Number of pages added _____ .

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